IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Kemmerer, Elizabeth
David BOTSTEIN, *et al.*	)	Art Unit: 1646
Application Serial No. 09/993,687	)	Confirmation No: 4943
Filed: November 14, 2001	)	Attorney's Docket No. 39780-2730 P1C11
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	)	**Customer No. 77845**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES
APPELLANTS' BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

This Appeal Brief, filed in connection with the above captioned patent application, is responsive to the Final Office Action mailed on September 19, 2007. A Notice of Appeal was filed herein on December 19, 2007. A request for a one-month extension of time is requested herewith. Appellants hereby appeal to the Board of Patent Appeals and Interferences from the final rejection in this case.

The following constitutes the Appellants' Brief on Appeal.

I. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the parent application, U.S. Patent Application Serial No. 09/941,992 recorded November 16, 2001, at Reel 012176 and Frame 0450.

II. RELATED APPEALS AND INTERFERENCES

The claims pending in the current application are directed to a polypeptide referred to herein as "PRO1009". There exist two related patent applications, (1) U.S. Patent Application Serial No. 09/991,181, now Patent No. 6, 913, 919, issued 07-05-2005 (containing claims directed to nucleic acids encoding PRO1009 polypeptides), and (2) U.S. Patent Application Serial No. 09/990,443, filed November 14, 2001 (containing claims directed to antibodies to PRO1009 polypeptides). Related U.S. Patent Application Serial No. 09/990,443 application is also under final rejection by the same Examiner and based upon the same outstanding rejections, an appeal is being pursued independently and concurrently herewith.

III. STATUS OF CLAIMS

Claims 119-126 and 129-131 are in this application.

Claims 1-118 and 127-128 have been canceled.

Claims 119-126 and 129-131 stand rejected and Appellants appeal the rejection of these claims.

A copy of the rejected claims in the present Appeal is provided as Claims Appendix (Section VIII).

IV. STATUS OF AMENDMENTS

A summary of the prosecution history for this case is as follows:

Previously, in response to a Final Office Action mailed on September 27, 2006 and October 13, 2006, a Notice of Appeal was filed March 13, 2007 and an Appeal Brief was filed June 13, 2007. This was followed by another Final Office action mailed September 19, 2007, wherein the finality of the previous Office Action was withdrawn by the Examiner. A Notice of Appeal was filed on December 19, 2007 in this case.

No claim amendments have been submitted after the last final rejection of September 19, 2007. A copy of the rejected claims in the present Appeal is provided as Appendix A.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The invention claimed in the present application is related to an isolated polypeptide comprising the amino acid sequence of the polypeptide of SEQ ID NO:194, referred to in the present application as "PRO1009." The PRO1009 gene was shown for the first time in the present application to be significantly amplified in human colon cancers as compared to normal, non-cancerous human tissue controls (Example 170). This feature is specifically recited in Claim 124, and carried by all claims dependent from Claim 124. In addition, the invention also claims the amino acid sequence of the polypeptide of SEQ ID NO:194, lacking its associated signal-peptide; or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209977 (Claims 124-126 and 129). The invention is further directed to polypeptides having at least 80% to 99% amino acid sequence identity to the amino acid sequence of the polypeptide of SEQ ID NO:194; the amino acid sequence of the polypeptide of SEQ ID NO:194, lacking its associated signal peptide; or the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209977, wherein the nucleic acid encoding said polypeptide is amplified in colon tumor (Claims 119-123). The invention is further directed to a chimeric polypeptide comprising one of the above polypeptides fused to a heterologous polypeptide (Claim 130), and to a chimeric polypeptide wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin (Claim 131). PRO polypeptide variants having at least about 80-99% amino acid sequence identity with a full length PRO polypeptide sequence, or a PRO polypeptide sequence lacking the signal peptide are generally described in the specification at, for example, page 305, line 23 onwards, and percent amino acid sequence identity determination is generally described at least at, for example, pages 306-308, line 14 onwards. The preparation of chimeric PRO polypeptides (Claims 130 and 131), including those wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin, is set forth in the specification at page 374, lines 24 to page 375, line 9. Examples 140-143 and page 376, line 12 onwards describe the expression of PRO polypeptides in various host cells, including *E. coli*, mammalian cells, yeast and Baculovirus-infected insect cells.

The amino acid sequence of the native "PRO1009" polypeptide and the nucleic acid sequence encoding this polypeptide (referred to in the present application as "DNA57129-1413") are shown in the present specification as SEQ ID NOs: 194 and 193, respectively, and in

Figures 121 and 122, described on pages 293, lines 23-26. The full-length PRO1009 polypeptide having the amino acid sequence of SEQ ID NO:194 is described in the specification at, for example, on page 15 and pages 116-118 and the isolation of cDNA clones encoding PRO1009 of SEQ ID NO:194 is described in Example 51, page 444-445 of the specification.

Finally, Example 170, in the specification at page 539, line 19, to page 555, line 5, sets forth a 'Gene Amplification assay' which shows that the PRO1009 gene is amplified in the genome of certain human colon cancers (see Table 9B, page 552-553). The profiles of various primary colon tumors used for screening the PRO polypeptide compounds of the invention in the gene amplification assay are summarized on Table 8, page 546 of the specification.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

1. Whether Claims 119-126 and 129-131 satisfy the utility/ enablement requirement under 35 U.S.C. §§101/112, first paragraph.
2. Whether Claims 119-123 and 130-131 satisfy the written description requirement under 35 U.S.C. §112, first paragraph.

VII. ARGUMENTS

Summary of the Arguments

Issue 1: Utility/Enablement

Appellants rely upon the gene amplification data of the PRO1009 gene for patentable utility of the PRO1009 polypeptides. This data is clearly disclosed in the instant specification in Example 170 which discloses that the gene encoding PRO1009 showed significant amplification, ranging from **2.085 fold to 4.287-fold** in **twelve** different colon primary tumors.

Appellants have submitted, in their Response filed August 4, 2005, a Declaration by Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of colon cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

Appellants have also submitted, in their Response filed June 18, 2004, ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded

protein will be expressed at an elevated level. First, the articles by Ornoft *et al.*, Hyman *et al.*, and Pollack *et al.* collectively teach that in general, gene amplification increases mRNA expression.

Appellants further submit that even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Appellants expressly do not concede), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Appellants submit that, as evidenced by the Ashkenazi Declaration and the teachings of Hanna and Mornin (both made of record in Appellants' Response filed June 18, 2004), simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu.

Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (*i.e.*, that it is more likely than not informative of the protein level). Therefore, as a general rule, one skilled in the art would find it more likely than not that PRO1009 is useful as a diagnostic tool for detecting colon tumors.

As the Examiner no longer questions whether mRNA levels are not predictive of polypeptide levels, the evidence presented by Appellants support that gene amplification correlates with the increased protein expression. Based on the from **2.085 fold to 4.287-fold** in **twelve** different colon primary tumors, one of ordinary skill would find it credible that the claimed PRO1009 polypeptides would have utility as markers for the diagnosis of colon tumors, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy.

Further, Appellants submit that one of ordinary skill in the art would know how to make and use the recited polypeptides for the diagnosis of colon cancer without any undue experimentation, based on the detailed teachings in the specification.

Accordingly, this enablement rejection under 35 U.S.C. §§101 and 112, first paragraph should be withdrawn.

Issue 2: Written Description

The factors to be considered in evidencing possession of a claimed genus include "disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof." Current applicable case law holds that biological sequences are not adequately described solely by a description of their desired functional activities. It is, however, well established that a combination of functional and structural features suffices to describe a claimed genus, as discussed in the PTO's own Written Description Guidelines, and as set forth in *Enzo Biochem., Inc. v. Genprobe, Inc.* Appellants note that the claims recite structural features, namely, 80-99% sequence identity to the native sequence of SEQ ID NO:194, which are common to the genus. The genus of claimed polypeptides is further defined by having a specific functional activity for the encoding nucleic acids, namely, that the encoding nucleic acid is amplified in colon tumors. The specification provides detailed guidance as to how to identify the recited variants of SEQ ID NO:194, including methods for determining percent identity between two amino acid sequences, as well as listings of exemplary and preferred sequence substitutions, as well as detailed protocols for determining whether a gene encoding a variant PRO1009 protein is amplified in colon tumor. Thus, one of skill in the art could easily identify whether a variant PRO1009 sequence falls within the parameters of the claimed invention.

Accordingly, a description of the claimed genus has been achieved by the recitation of both structural and functional characteristics.

These arguments are all discussed in further detail below under the appropriate headings.

Response to Rejections

ISSUE 1. Claims 119-126 and 129-131 are Supported by a Credible, Specific and Substantial Asserted Utility, and Thus, Meet the Utility Requirement of 35 U.S.C. §§101/112, First Paragraph

The sole basis for the Examiner's rejection of Claims 119-126 and 129-131 under this section is that the data presented in Example 170 of the present specification is allegedly insufficient under the present legal standards to establish a patentable utility under 35 U.S.C. §101 for the presently claimed subject matter.

Claims 119-126 and 129-131 stand further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted

utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

Appellants strongly disagree and, therefore, respectfully traverse the rejection.

A. The Legal Standard For Utility Under 35 U.S.C. §101

According to 35 U.S.C. §101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added).

In interpreting the utility requirement, in *Brenner v. Manson,*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent Applicant disclose a "substantial utility" for his or her invention, *i.e.*, a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler,*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The Court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

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[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

In *Cross v. Iizuka,*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The Court perceived, "No insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."[8]

The case law has also clearly established that Appellants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial burden to prove that Appellants' claims of usefulness are not believable on their face.[10] In general, an Appellant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11,12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the

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[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) *cert. denied,* 469 US 835 (1984).

totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the Appellant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines"),[15] which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the Applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

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[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II(B)(1).

B. Proper Application of the Legal Standard

Appellants submit that the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the Appellant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant.

Appellants respectfully submit that the data presented in Example 170 starting on page 539 of the specification of the specification and the cumulative evidence of record, which underlies the current dispute, indeed support a "specific, substantial and credible" asserted utility for the presently claimed invention.

Patentable utility for the PRO1009 polypeptides is based upon the gene amplification data for the gene encoding the PRO1009 polypeptide. Example 170 describes the results obtained using a very well-known and routinely employed polymerase chain reaction (PCR)-based assay, the TaqMan™ PCR assay, also referred to herein as the gene amplification assay. This assay allows one to quantitatively measure the level of gene amplification in a given sample, say, a tumor extract, or a cell line. It was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. Appellants isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9 (pages 539 onwards of the specification), including primary colon cancers of the type and stage indicated in Table 8 (page 546). The tumor samples were tested in triplicates with Taqman™ primers and with internal controls, beta-actin and GADPH in order to quantitatively compare DNA levels between samples (page 548, lines 33-34). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29) and also, no-template controls (page 548, lines 33-34). The results of TaqMan™ PCR are reported in ΔCt units, as explained in the passage on page 539, lines 37-39. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on. Using this PCR-based assay, Appellants showed that the gene encoding for PRO1009 was amplified, that is,

it showed approximately 1.06-2.10 ΔCt units which corresponds to $2^{1.06}$ -$2^{2.10}$- fold amplification or **2.085 fold to 4.287-fold** in twelve different colon primary tumors.

In support of their showing that these gene amplification values are significant, Appellants submitted, in the RCE filed August 4, 2005, a Declaration by Dr. Audrey Goddard. Appellants particularly draw the Board's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.
> (Emphasis added).

Appellants point out that the Declaration by Dr. Audrey Goddard provides a statement by an expert in the relevant art that "fold amplification" values of at least 2-fold are considered significant in the TaqMan™ PCR gene amplification assay. Appellants particularly draw the Board's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy.
> (Emphasis added).

Accordingly, the **2.085 fold to 4.287-fold** in **twelve** different colon primary tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed in the Goddard Declaration. As any skilled artisan in the field of oncology would easily appreciate that this gene is a good candidate marker for diagnosing colon tumors and

would clearly find utility for the PRO1009 gene as a diagnostic for colon cancer or for diagnosing individuals at risk for developing colon cancer.

The Examiner has also alleged, based on Sen *et al.*, that the observed gene amplification was not corrected for aneuploidy. The Examiner has also asserted it is not clear whether PRO1009 is amplified in cancerous colon tissue more than in damaged colon tissue. (Page 3 of the Office Action mailed September 19, 2007)

Appellants respectfully disagree and submit that their gene amplification data was not due to aneuploidy. Appellants had submitted the Ashkenazi Declaration to show that "detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy." Regarding Sen, Appellants agree that while aneuploidy can be a feature of damaged tissue as well, besides cancerous or pre-cancerous tissue, and may not invariably lead to cancer, Sen *et al.* in fact support the Appellants' position that PRO1009 is still useful in diagnosing pre-cancerous lesions or cancer itself. For instance, the art in colon cancer at the time of filing of the instant application clearly described that "epithelial tumors develop through a multistep process driven by genetic instability" in damaged colon lesions which may eventually lead to colon cancer. Many articles published around June 23, 1999 (the effective filing date of this application) studied such damaged or premalignant lesions and suggested that identification of such pre-cancerous lesions were very important in preventive diagnosis and treatment of colon cancer. Based on the well-known art, Appellants submit that there is utility in identifying genetic biomarkers in epithelial tissues at cancer risk.

C. A *prima facie* case of lack of utility has not been established

The Examiner has asserted, based on Pennica *et al.*, Konopka *et al.*, Godbout *et al.*, and Li *et al.* that there is a general lack of correlation between gene amplification and mRNA expression, and, thus, the data in Table 9, while may provide a basis for utility and enablement of PRO1009 nucleic acid, does not provide a basis for utility or enablement of the claimed polypeptides (Pages 5-7 of the Final Office Action mailed September 19, 2007).

As a preliminary matter, Appellants respectfully submit that it is not a legal requirement to establish that gene amplification "necessarily" results in increased expression at the mRNA and polypeptide levels or that polypeptide levels can be "accurately predicted." As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent

application is a preponderance of the totality of the evidence under consideration. Accordingly, Appellants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Appellants submit that Pennica *et al.* does not show a lack of correlation between gene (DNA) amplification and mRNA levels. According to the quoted statement from Pennica *et al.*, "WISP-1 gene amplification in human colon tumors showed a correlation between DNA amplification and over-expression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased polypeptide expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . ." (Pennica *et al.*, page14722, left column, first full paragraph, emphasis added).

Accordingly, Appellants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-expression of the encoded WISP polypeptide. More importantly, the teaching of Pennica *et al.* is specific to *WISP* genes. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression in general.

Similarly, in Konopka *et al.*, Appellants submit that the Examiner has generalized a very specific result disclosed by Konopka *et al.* to cover all genes. Konopka *et al.* actually state that "[p]rotein expression is not related to amplification of the ***abl*** gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph^1 template." (See Konopka *et al* ., Abstract, emphasis added). The paper does not teach anything whatsoever about the correlation of protein expression and gene amplification in general, and provides no basis for the generalization that apparently underlies the present rejection. The statement of Konopka *et al.* that "[p]rotein expression is not related to amplification of the *abl* gene . . . " is not sufficient to establish a *prima facie* case of lack of utility. Therefore, the combined teachings of Pennica *et al.* and Konopka *et al.* are not directed towards genes in general but to a single gene or genes within a single family and thus, their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or protein levels.

The Examiner has asserted that unlike Godbout *et al.*, the instant specification does not teach structure/ function analysis and the Examiner questions whether the level of genomic amplification of DDX1 gene is comparable to that disclosed by PRO1009. The Examiner has further asserted that, there is no evidence in the present application that PRO1009 confers growth advantage to the cells. (Page 7 of the Office Action mailed in September 19, 2007)

Regarding the Godbout reference, Appellants respectfully submit that it was never claimed that PRO1009 is similar in any way to the DDX1 gene of Godbout *et al.,* they never claimed PRO1009 was an RNA helicase or that it confers selective advantage to cell survival; on the other hand, the Godbout reference was submitted to show good correlation between protein levels based upon genomic DNA amplification, which the Examiner clearly agrees with. Moreover, selective advantage to cell survival is not the only mechanism by which genes impact cancer. Structure/function data, which the Examiner requests, is not a requirement for the utility requirement. Hence this rejection is improper.

The Examiner has cited Li *et al.* as teaching that "68.8% of the genes showing over-representation in the genome did not show elevated transcript levels." ((Page 7 of the Office Action mailed in September 19, 2007)

Appellants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The

authors note that "[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma" (page 2629, col. 1). For instance, as explained in the Supplemental Information accompanying the Li article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. In the case of PRO1009, as discussed in previously filed responses and in the Goddard Declaration (of record), an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0 (which is a higher threshold). The PRO1009 gene showed significant amplification of **2.085 fold to 4.287-fold** in twelve different colon primary tumors, and thus fully meets this standard. It is not surprising that in the Li *et al.* reference, by using a lower threshold of 1.4 for considering gene amplification, a higher number of genes not showing corresponding increases in mRNA expression were found. Moreover, Appellants add that the results of Li *et al.* do not conclusively disprove that a gene with a substantially higher level of gene amplification, such as PRO1009, would be expected to show a corresponding increase in transcript expression.

It is "more likely than not" for amplified genes to have increased mRNA

On the contrary, Appellants submit that Example 170 of the specification further discloses that, "(a)mplification is associated with overexpression of the gene product, indicating that the polypeptides are useful targets for therapeutic intervention in certain cancers such as lung, colon, breast and other cancers and diagnostic determination of the presence of those cancers" (Emphasis added). Besides, Appellants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is "more likely than not" that the corresponding mRNA will also be expressed at an elevated level.

For instance, Appellants presented the articles by Ornfoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in Appellants' Response filed August 2, 2006 or Response filed June 4, 2004), who collectively teach that in general, for most genes, DNA amplification increases mRNA expression. The results presented by Ornfoft *et al.*, Hyman *et al.*, and Pollack *et al.* are based upon wide ranging analyses of a large number of tumor associated genes. Ornfoft *et al.* studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material, and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding

increase in mRNA transcripts. Hyman *et al.* compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. In Pollack *et al.*, the authors profiled DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that on average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold change in mRNA levels. In summary, the evidence supports the Appellants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip® arrays in 2004. Clearly, the research community believe that the information obtained from these chips is useful (*i.e.*, that it is more likely than not that the results are informative of protein levels).

Thus, the Examiner appears to disregard the ample evidence provided in the above referenced articles based on misinterpretations of their teachings. Appellants submit that in fact, these articles lend significant support that for an amplified gene, it is more likely than not that the protein will also be overexpressed and would be viewed as reasonable and credible by one of ordinary skill in the art. The "more likely than not" standard is a much lower standard than a "necessary" correlation or "accurate" prediction, and is clearly met in the claimed invention. Moreover, the Examiner has not cited any evidence or advanced any arguments as to why Appellants' statement of overexpression of protein would not be credible. Accordingly, this point is believed to be moot.

The Examiner has stated that Appellants have not indicated whether PRO1009 is in a gene cluster region of a chromosome. (Page 7 of the Office Action mailed September 19, 2007). Appellants fail to see how this is relevant to the analysis. Orntoft *et al.* did not limit their findings to only those regions of amplified gene clusters. Further, as discussed below, Hyman *et al.* and Pollack *et al.* did gene-by-gene analysis across all chromosomes.

Appellants respectfully submit that the Examiner has mischaracterized the methods used by Hyman *et al.* and Pollack *et al* in their analysis. These papers did not use traditional CGH analysis to identify amplified genes. In Hyman *et al.*, 13,824 cDNA clones were placed on glass

slides in a microarray and genomic DNA from breast cancer cell lines and normal human WBCs was hybridized to the cDNA sequences. For expression analysis, RNA from tumor cell lines was hybridized on the same microarrays. The 13,824 arrayed cDNA clones were analyzed for gene expression and gene copy number in 14 breast cancer cell lines. Hyman *et al.* state, "The results illustrate a considerable influence of copy number on gene expression patterns." For example, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e.*, belonged to the global upper 7% of expression ratios) compared with only 6% for genes with normal copy number." (See page 6242, column 1). Further, Hyman *et al.* state that "[t]he cDNA/CGH microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome." (See page 6242, column 2). Therefore, the analysis performed by Hyman *et al.* was on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

In Pollack *et al.*, DNA copy number alteration across 6,691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines was profiled. Pollack *et al.* further state, "Parallel microarray measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells." (See Abstract). "Genome-wide, of 117 high-level DNA amplifications (fluorescence ratios >4, and representing 91 different genes), 62% (representing 54 different genes; ...) are found associated with at least moderately elevated mRNA levels (mean-centered fluorescence ratios >2), and 42% (representing 36 different genes) are found associated with comparably highly elevated mRNA levels (mean-centered fluorescence ratios >4)." (See page 12966, column 1). Therefore, the analysis performed by Pollack *et al.* was also on a gene-by gene basis, and clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

The Examiner has further asserted that "none of the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics" (Page 12 of the Office Action mailed September 19, 2007). Appellants respectfully point out that Hyman *et al.* conducted additional studies of one of the genes found to be amplified, HOXB7, and found "a clinical association between HOXB7 amplification and poor patient prognosis." (Page 6244, col.1 to col.2). Thus the results of Hyman *et al.* confirm that genes which are amplified in

tumors have prognostic utility. The Board's attention is also respectfully directed to the final paragraph of Pollack *et al.*, wherein the authors conclude that "a substantial portion of the phenotypic uniqueness (and, by extension, the heterogeneity in clinical behavior) among patients' tumors may be traceable to underlying variation in DNA copy number." (Page 12698, col. 2). Accordingly, Pollack *et al.* confirm that genes that are amplified in at least one type of tumor are useful as markers for that type of tumor, and for prognostic uses directed to that type of tumor.

Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which Appellants submit is **not** true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a specific, substantial, and credible utility. In support, Appellants respectfully draw the Board's attention to page 2 of the Declaration of Dr. Avi Ashkenazi (submitted with the Response filed August 4, 2004) which explains that,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Appellants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient

with agents that target that gene product. This not only saves money, but also has the benefit that the patient can avoid exposure to the side effects associated with such agents.

This utility is further supported by the teachings of the article by Hanna and Mornin. (Pathology Associates Medical Laboratories, August (1999), submitted with the Response filed June 4, 2004). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinomas. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Examiner has asserted that "Hanna et al. supports the rejection, in that Hanna et al. show that gene amplification does not reliably correlate with protein over-expression, and thus the level of polypeptide expression must be tested empirically." (Page 17 of the Office Action mailed September 19, 2007). Appellants respectfully point out that the Examiner appears to have misread Hanna *et al.* Hanna *et al.* clearly state that gene amplification (as measured by FISH) and polypeptide expression (as measured by immunohistochemistry, IHC) are well correlated ("in general, FISH and IHC results correlate well" (Hanna *et al.* p. 1, col. 2)). It is only a subset of tumors which show discordant results. Thus Hanna *et al.* support Appellants' position that it is more likely than not that gene amplification correlates with increased polypeptide expression.

Appellants have clearly shown that the gene encoding the PRO1009 polypeptide is amplified in at least two colon tumors. Therefore, the PRO1009 gene, similar to the HER-2/neu gene disclosed in Hanna *et al.*, is a tumor associated gene. Furthermore, as discussed above, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO1009 gene, that the PRO1009 polypeptide is concomitantly overexpressed.

The Examiner appears to view the testing described in the Ashkenazi Declaration and the Hanna article as experiments involving further characterization of the PRO1009 polypeptide itself. In fact, such testing is for the purpose of characterizing not the PRO1009 polypeptide, but

the tumors in which the gene encoding PRO1009 is amplified. The PRO1009 polypeptide and the claimed antibodies which bind it are therefore useful in tumor categorization, the results of which become an important tool in the hands of a physician enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient.

Thus, based on the asserted utility for PRO1009 in the diagnosis of selected colon tumors, the reduction to practice of the instantly claimed protein sequence of SEQ ID NO:194 in the present application, the disclosure of the step-by-step protocols for making chimeric PRO polypeptides, including those wherein the heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin in the specification (at page 374, lines 24 to page 375, line 9), the disclosure of a step-by-step protocol for making and expressing PRO1009 in appropriate host cells (in Examples 140-143 and page 376, line 12), the step-by-step protocol for the preparation, isolation and detection of monoclonal, polyclonal and other types of antibodies against the PRO1009 protein in the specification (at pages 390-395) and the disclosure of the gene amplification assay in Example 170, the skilled artisan would know exactly how to make and use the claimed polypeptide for the diagnosis of colon cancers. Appellants submit that based on the detailed information presented in the specification and the advanced state of the art in oncology, the skilled artisan would have found such testing routine and not 'undue'.

Therefore, Appellants respectfully request reconsideration and reversal of this outstanding rejections under 35 U.S.C. §101 and §112, First Paragraph to Claims 119-126 and 129-131.

ISSUE 2: Claims 119-123, 130 and 131 Satisfy the Written Description Requirement of 35 U.S.C. §112, First Paragraph

Claims 119-123, 130 and 131 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing "subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." In particular, the Examiner has asserted that "the specification does not (disclose) any variants of SEQ ID NO: 194, naturally occurring or not, nor whether such sequences are amplified in colon tumors" (Page 14, Final Office Action mailed September 7, 2005). The Examiner also cites *Fiers v. Revel*, 25

*U.S.P.Q.*2d 1601 (Fed. Cir. 1993) and *Fiddes v. Baird*, 30 *U.S.P.Q.*2d 1481, 1483 (1993) to show that .

Appellants respectfully disagree.

A. The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[18,19] The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[20] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure.[21,22]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[23] the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field."[24] Further, the "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity

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[18] *In re Kaslow*, 707 F.2d 1366, 1374, 212 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983).

[19] *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116 (Fed. Cir. 1991).

[20] *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 U.S.P.Q.2d at 1116.

[21] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[22] *See also* M.P.E.P. §2163 II(A).

[23] 713 F.2d 693, 696, 218 U.S.P.Q. 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

[24] *See also* M.P.E.P. §2141.03.

have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[25, 26]

B. The Disclosure Provides Sufficient Written Description for the Claimed Invention

Appellants respectfully submit that the instant specification evidences the actual reduction to practice of the native amino acid sequence of SEQ ID NO: 194. Support for "native sequences" can be found in the instant specification at least at page 304, line 26. Appellants also submit that the specification provides ample written support for determining percent sequence identity between two amino acid sequences (See pages 306-308, line 14 onwards). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 372, line 36 to page 373, line 17). This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 372). Accordingly, one of skill in the art could identify whether the variant PRO1009 sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specification sets forth methods for making the amino acid sequences (see page 376, line 9) and methods of preparing the PRO polypeptides (see Examples 140-143).

Currently pending Claims 119-123 and 130-131 recite the functional recitation that the nucleic acid encoding the claimed polypeptides are amplified in colon tumors. Appellants further submit that the specification provides ample written support for detecting and quantifying amplification of such nucleic acids in several tumors and/or cell lines as described in Example 170. Example 170 of the present application provides step-by-step guidelines and protocols for the gene amplification assay. By following this disclosure, one skilled in the art

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[25] *Ex parte Hiyamizu*, 10 U.S.P.Q.2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[26] See *also* M.P.E.P. §2141.03.

would know that it is easy to test whether a gene encoding a variant PRO1009 protein is amplified in colon tumors by the methods set forth in Example 170.

Appellants refer to the arguments and information presented above in response to the outstanding rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, for alleged lack of utility and enablement. These arguments are incorporated by reference herein. Appellants respectfully submit that as discussed above under Issue I, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Goddard Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, the amplification of the encoding polynucleotide in tumors does provide useful information regarding the functional property of the polypeptide in being overexpressed in tumor tissues.

Appellants further respectfully submit that whether or not the polypeptide is also overexpressed in tumor tissues is irrelevant to the consideration of adequate written description. The claims have characterized the recited polypeptides as having the property that their encoding polynucleotides are amplified in colon tumors. As discussed above, the specification describes methods for identifying genes which are amplified in colon tumors. Therefore, one of skill in the art could readily test a nucleic acid sequence which encodes a variant polypeptide to determine whether it is amplified by the methods set forth in Example 170. Thus, the recited property of amplification of the encoding gene adds to the characterization of the claimed polypeptide sequences in a manner that one of skill in the art could readily assess and understand.

Applicants respectfully submit that the issue is whether the claimed sequences are adequately described. Appellants respectfully submit that the full-length sequence of PRO1009 is clearly provided in the specification. The Examiner has acknowledged that the specification discloses the full-length sequence of SEQ ID NO:194 and that polypeptides comprising the sequence set forth in SEQ ID NO:194 meet the written description provision of 35 U.S.C. §112, first paragraph.

Secondly, Appellants submit that the court in *Fiers v. Revel* held that "[i]f a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, as we have held, then a description also requires that degree of specificity." *Fiers*, 984 F.2d at 1171. Since the instant claims are directed to polypeptides, *Fiers* is distinguished on the facts and does not apply. Similarly, the *Fiddes* decision holds that naturally-occurring gene sequences cannot be patented unless the actual sequence is clearly disclosed in the patent

application. Again, since the instant claims are directed to polypeptides, *Fiddes* is distinguished on the facts and does not apply.

In *Fiddes v. Baird*, the Board of Patent Appeals and Interferences held that party Fiddes' claims to a human gene for basic fibroblast growth factor were separately patentable over party Baird's issued and pending claims specifying a sequence encoding "mammalian" basic fibroblast growth factor. Party Baird's issued patent disclosed the amino acid sequence that had been isolated from bovine pituitary and a theoretical DNA sequence encoding it. Party Baird's pending claims were from a continuation-in-part application disclosing the naturally-occurring coding sequence for bovine fibroblast growth factor. Between the filing of the first application and the continuation-in-part application, DNA sequences anticipating claims to the naturally-occurring human fibroblast growth factor were published. Party Baird argued that the published sequence could not be used as prior art because it was entitled to the filing date of the first application.

The Board held that party Baird was not entitled to the filing date of the first application of its claims to the mammalian DNA sequence because it did not set out specific DNA sequences of naturally-occurring mammalian genes in the first application. Therefore, the first application did not meet the "written description" for the specific DNA sequences of naturally-occurring mammalian genes. The Board added that party Baird was not in possession of the naturally occurring bovine gene at the time of filing the first application even though its encoded amino acid sequence was known.

Appellants respectfully submit that in the present application, Appellants have clearly disclosed the full-length sequence of SEQ ID NO:194 and its encoding nucleic acid sequence SEQ ID NO:193. In addition, one of skill in the art could identify whether the variant PRO1009 sequence falls within the parameters of the claimed invention. Furthermore, as mentioned above, since the instant claims are directed to polypeptides, *Fiddes* is distinguished on the facts and does not apply. Accordingly, the Examiner's assertion that Appellants provide no written description in the specification for any other species of PRO1009 molecules is based on the incorrect interpretation of the holding in the *Fiddes* case.

More recently, in *Enzo Biochem., Inc. v. Genprobe, Inc.* 296 F.3d 1316 (Fed. Cir. 2002), the court adopted the standard that "the written description requirement can be met by showing that the invention is complete by disclosure of sufficiently detailed, relevant identifying

characteristics, . . . *i.e.,* complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324. While the invention in *Enzo* was still a DNA, the holding has been treated as being applicable to proteins as well. Indeed, the court adopted the standard from the USPTO's Written Description Examination Guidelines, which apply to both proteins and nucleic acids.

Accordingly, current applicable case law holds that biological sequences are not adequately described **solely** by a description of their desired functional activities. The instant claims meet the standard set by the *Enzo* court in that the claimed sequences are defined not only by functional properties, but also by structural limitations. It is well established that a **combination** of functional and structural features may suffice to describe a claimed genus. "An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, *i.e.,* complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."[27] Thus, the genus of polypeptides with at least 80-99% sequence identity to SEQ ID NO:194, which possess the functional property of having a nucleic acid which is amplified in colon tumor would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description. Accordingly, one skilled in the art would have known that Appellants had knowledge and possessed the claimed polypeptides with 80-99% sequence identity to SEQ ID NO: 194 whose encoding nucleic acids were amplified in colon tumors. The recited property of amplification of the encoding gene adds to the characterization of the claimed polypeptide sequences in a manner that one of skill in the art could readily assess and understand. As discussed above, Appellants have recited structural features, namely, 80-99% sequence identity to SEQ ID NO: 194, which are common to the genus. Appellants have also provided guidance as to how to make the recited variants of SEQ ID NO:194, including listings of exemplary and preferred sequence substitutions. The genus of claimed polypeptides is further defined by having a specific

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[27] M.P.E.P. §2163 II(A)(3)(a).

functional activity for the encoding nucleic acids. Accordingly, a description of the claimed genus has been achieved.

Accordingly, Appellants respectfully request reconsideration and reversal of the written description rejection of Claims 119-123 and 130-131 under 35 U.S.C. §112, first paragraph.

CONCLUSION

For the reasons given above, Appellants submit that present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification clearly teaches "how to use" the presently claimed polypeptide. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejection of Claims 119-126 and 129-131.

The Commissioner is authorized to charge any fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. **07-1700** (referencing Attorney's Docket No. **39780-2730 P1C11**).

Respectfully submitted,

Date: March 19, 2008

By:_____
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VIII. CLAIMS APPENDIX

Claims on Appeal

119. An isolated native sequence polypeptide having at least 80% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO: 194;

(b) the amino acid sequence of the polypeptide of SEQ ID NO: 194, lacking its associated signal peptide;

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209977,

wherein, the nucleic acid encoding said polypeptide is amplified in colon tumors.

120. The isolated native sequence polypeptide of Claim 119 having at least 85% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO: 194;

(b) the amino acid sequence of the polypeptide of SEQ ID NO: 194, lacking its associated signal peptide;

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209977,

wherein, the nucleic acid encoding said polypeptide is amplified in colon tumors.

121. The isolated native sequence polypeptide of Claim 119 having at least 90% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO: 194;

(b) the amino acid sequence of the polypeptide of SEQ ID NO: 194, lacking its associated signal peptide;

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209977,

wherein, the nucleic acid encoding said polypeptide is amplified in colon tumors.

122. The isolated native sequence polypeptide of Claim 119 having at least 95% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO: 194;

(b) the amino acid sequence of the polypeptide of SEQ ID NO: 194, lacking its associated signal peptide;

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209977,

wherein, the nucleic acid encoding said polypeptide is amplified in colon tumors.

123. The isolated native sequence polypeptide of Claim 119 having at least 99% amino acid sequence identity to:

(a) the amino acid sequence of the polypeptide of SEQ ID NO: 194;

(b) the amino acid sequence of the polypeptide of SEQ ID NO: 194, lacking its associated signal peptide,

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209977,

wherein, the nucleic acid encoding said polypeptide is amplified in colon tumors.

124. An isolated polypeptide comprising:

(a) the amino acid sequence of the polypeptide of SEQ ID NO: 194;

(b) the amino acid sequence of the polypeptide of SEQ ID NO: 194, lacking its associated signal peptide,

(c) the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209977,

wherein, the nucleic acid encoding said polypeptide is amplified in colon tumors.

125. The isolated polypeptide of Claim 124 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 194.

126. The isolated polypeptide of Claim 124 comprising the amino acid sequence of the polypeptide of SEQ ID NO: 194, lacking its associated signal peptide.

129. The isolated polypeptide of Claim 124 comprising the amino acid sequence of the polypeptide encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209977.

130. A chimeric polypeptide comprising a polypeptide according to Claim 124 fused to a heterologous polypeptide.

131. The chimeric polypeptide of Claim 130, wherein said heterologous polypeptide is an epitope tag or an Fc region of an immunoglobulin.

IX. EVIDENCE APPENDIX

1. Declaration of Audrey Goddard, Ph.D. under 35 C.F.R. §1.132, with attached Exhibits A-G:

   A. Curriculum Vitae of Audrey D. Goddard, Ph.D.
   B. Higuchi, R. *et al.*, "Simultaneous amplification and detection of specific DNA sequences," *Biotechnology* 10:413-417 (1992).
   C. Livak, K.J., *et al.*, "Oligonucleotides with fluorescent dyes at opposite ends provide a quenched probe system useful for detecting PCR product and nucleic acid hybridization," *PCR Methods Appl.* 4:357-362 (1995).
   D. Heid, C.A. *et al.*, "Real time quantitative PCR," *Genome Res.* 6:986-994 (1996).
   E. Pennica, D. *et al.*, "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors," *Proc. Natl. Acad. Sci. USA* 95:14717-14722 (1998).
   F. Pitti, R.M. *et al.*, "Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer," *Nature* 396:699-703 (1998).
   G. Bieche, I. *et al.*, "Novel approach to quantitative polymerase chain reaction using real-time detection: Application to the detection of gene amplification in breast cancer," *Int. J. Cancer* 78:661-666 (1998).

2. Declaration of Avi Ashkenazi, Ph.D. under 35 C.F.R. §1.132, with attached Exhibit A (Curriculum Vitae).

3. Orntoft, T.F., et al., "Genome-wide Study of Gene Copy Numbers, Transcripts, and Protein Levels in Pairs of Non-Invasive and Invasive Human Transitional Cell Carcinomas," *Molecular & Cellular Proteomics* **1**:37-45 (2002).

4. Hyman, E., *et al.*, "Impact of DNA Amplification on Gene Expression Patterns in Breast Cancer," *Cancer Research* 62:6240-6245 (2002).

5. Pollack, J.R., *et al.*, "Microarray Analysis Reveals a Major Direct Role of DNA Copy Number Alteration in the Transcriptional Program of Human Breast Tumors," *Proc. Natl. Acad. Sci. USA* 99:12963-12968 (2002).

6. Hanna *et al.*, "HER-2/neu Breast Cancer Predictive Testing," Pathology Associates Medical Laboratories (1999).

7. Pennica, D. et al., "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in human colon tumors," *Proc. Natl. Acad. Sci. USA* **95**:14717-14722 (1998).

8. Konopka *et al.*, "Variable Expression of the Translocated c-abl oncogene in Philadelphia-chromosome-positive B-lymphoid cell lines from chronic myelogenous leukemia patients" *Proc. Natl. Acad. Sci. USA* 83: 4049-52, (1986).

9. Godbout, R., *et al.*, J Biol Chem, - 273(33):21161-8 (1998).

10. Li *et al.*, 2006, Oncogene 25: 2628-2635.

11. Sen *et al.* , Current Opinion in Oncology, 12: 82-88, (2000).

Item 1 was submitted with Appellants' Response filed August 4, 2005, and was considered by the Examiner as indicated in the Final Office Action mailed September 7, 2005.

Items 2-6 were submitted with Appellants' Response filed June 18, 2004, and were considered by the Examiner as indicated in the Final Office Action mailed September 16, 2004.

Items 7-8 were made of record by the Examiner in the Office Action mailed March 19, 2004.

Item 9 was submitted with Appellants' Response filed June 29, 2006, and were considered by the Examiner as indicated in the Final Office Action mailed September 27, 2006.

Item 10 was made of record by the Examiner in the Final Office Action mailed October 13, 2006.

Item 11 was made of record by the Examiner in the Final Office Action mailed September 19, 2007.

X. RELATED PROCEEDINGS APPENDIX

None.

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